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2),^[11] and O-phenyl hydroxamates reported by Watson and co-workers in 2016 (Class 3).^[12] Each system exhibits prescriptive ligand requirements, although, in general, electron poor P-based ligands are required for efficient reactivity. Class 1 and Class 2 N–O donors cyclize via a cationic aza-Pd^{II} intermediate, access to which is driven by facile protodecarbonylation of the pentafluorobenzoate leaving group.^[10f] Given these considerations, we elected to evaluate the cyclization of O^FBz carbamate **2a** in the presence of Pd systems modified by weak donor ligands. Gratifyingly, we found that the target cyclization was feasible, and, for this non-demanding system, a variety of triarylphosphine ligands were reasonably effective using Pd₂(dba)₃ as the precatalyst (see the Supporting Information). Ultimately, the optimal system was PA-Ph (**L-1**, PA = 1,3,5,7-tetramethyl-2,4,8-trioxo-6-phosphaadamantany) and, using this ligand, we were able to access target **4a** in 85 % yield after optimization of other reaction parameters. **L-1** is a bulky and electron poor ligand, with the latter facet resulting from its constrained C–P–C bond angle and inductively withdrawing oxygen atoms.^[13] The bulky *tert*-butyl unit of **2a** is also beneficial, with less sterically demanding systems **2b** and **2c** cyclizing in lower but acceptable yields.

The efficacy of **L-1** prompted us to undertake the one-step synthesis of a variety of electronically tuned variants via arylation of commercially available PA-H (see the SI). These studies revealed that systems with electron withdrawing groups at the *para*-position of the aryl unit were especially effective, such that **L-2** and **L-3** emerged as complementary ligands for subsequent studies. Using this ligand set, we explored the scope of the catalyst system for 5-*exo* aza-Heck cyclizations and found it to be highly effective across a wide range of substrates (Table 1). Different carbamates are tolerated (**4a–d**), diastereoselective processes are readily achieved (**4f–h**), tetrasubstituted stereocenters can be constructed (**4i**, **4k**, and **4m**) and electron poor alkenes participate efficiently (**2j** to **4j**). The method is especially powerful for bicyclic ring construction; 5-*exo* cyclization onto exocyclic (**4k**) or cyclic (**4l**) alkenes provided complex perhydroindole scaffolds, and spiro (**4m**) or transannular (**4n**) C–N bond formations were also efficient. For demanding systems (e.g., **4i**) **L-2** or **L-3** provide 10–15 % higher yields than **L-1** (selected comparisons are given in the SI). The results in Table 1 show that the aza-Heck method offers far greater scope for 5-*exo* cyclizations than currently available aza-Wacker protocols.

Prior classes of aza-Heck process cannot achieve efficient 6-*exo* cyclizations of non-biased systems, and a solution to this issue represents a longstanding challenge of the area.^[5a] We were pleased to find that the present method addresses this, as demonstrated by the cyclizations of **2o** and **2p**, which occurred with good levels of efficiency to afford **4o** and **4p**, respectively (Table 2). More highly substituted systems can also be generated (e.g., **4s** and **4t**), with the method offering particularly good scope for the construction of tetrahydroisoquinolines (**4r** and **4u**), as well as unusual aza-variants (**4v** and **4w**). The process is effective for cyclizations involving both electron rich (**4r**) and electron poor (e.g. **4u**) alkenes. For these more demanding 6-*exo* cyclizations an *N*-Boc group

Table 1: Carbamate protected pyrrolidines by aza-Heck cyclization.

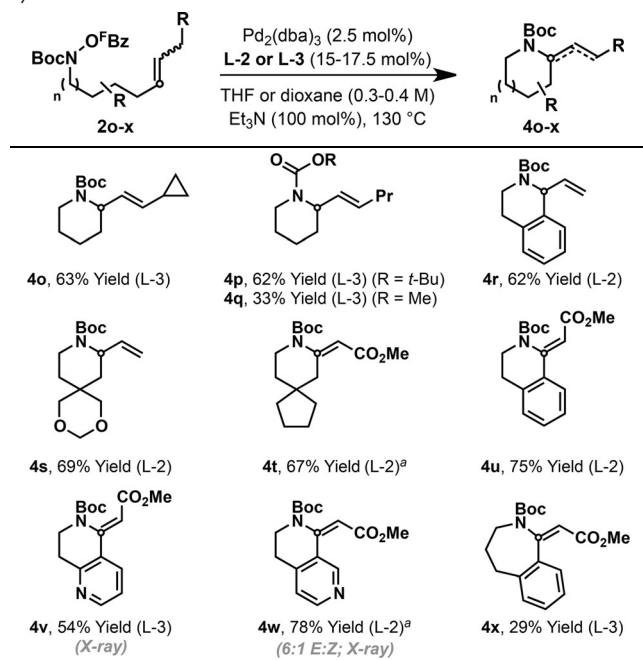
L-1: Ar = Ph	L-2: Ar = 4-CF ₃ C ₆ H ₄	L-3: Ar = 4-CO ₂ EtC ₆ H ₄
 4a , R = <i>t</i> -Bu, 85% Yield (L-1) 4b , R = <i>i</i> -Pr, 78% Yield (L-1) 4c , R = Me, 70% Yield (L-1)	 4d , 78% Yield (L-2)	 4e , 78% Yield (L-2)
 4f , 58% Yield ^a (L-3) (10:1 d.r.) 4g , 88% Yield (L-1) (4:1 d.r.)	 4h , 77% Yield ^a (L-3) (>20:1 d.r.)	
 4i , 87% Yield (L-2)	 4j , 95% Yield (L-1)	 4k , 92% Yield (L-2)
 4l , 78% Yield (L-2)	 4m , 81% Yield (L-2)	 4n , 64% Yield (L-1)

[a] Dioxane (0.3 M) was used as solvent. Alkene geometry of substrates: **2a**, *E*; **2b**, *E*; **2c**, *E*; **2d**, *E*; **2e**, 6:1 *E*:*Z*; **2f**, *E*; **2g**, *E*; **2h**, *E*; **2i**, *Z*; **2j**, *E*; **2k**, *E*.

is required; cyclization to afford methyl carbamate system **4q** occurred in only 33 % yield under optimized conditions. The use of PA-Ar ligand systems is also critical for the processes in Table 2, with **L-2** or **L-3** being the preferred variants. Triarylphosphines that were effective for 5-*exo* cyclization generated **4p** in less than 10 % yield (see the SI). The PA-Ar ligand system even enabled 7-*exo* cyclization to afford **4x**, albeit in modest yield.

For the processes described here, our collective observations are supportive of an aza-Heck pathway akin to that proposed for Class 1 and Class 2 N–O donors.^[10f, 11] Under optimized conditions, cyclization of O^FBz system **2k** in the presence of NH system **5** provided target **4k** in 79 % yield and aza-Wacker product **4a** was not observed (Scheme 2 A). This result confirms that the N–O bond acts as an internal oxidant only. Accordingly, N–O oxidative addition to **3** should be followed by *syn*-stereospecific amino-palladation of the alkene.^[14] Consistent with this, cyclization of *trans*-acrylate **2t** delivered adduct **4t** as a single geometric isomer, in which the alkene substituents that were present in the starting material are now in a *cis*-arrangement. The observed switch in geometry is consistent with a sequence of *syn*-amino-palladation and *syn*-β-hydride elimination (Scheme 2 B); a similar phenomenon is observed in the conventional Heck reaction.^[15] For the cyclization of **2u** and **2v**, this geometry inversion was not observed at full conversion, with **4u** and **4v** formed in > 25:1 *Z*:*E* ratios. However, when the cyclization of

Table 2: Carbamate protected heterocycles by 6- and 7-*exo* aza-Heck cyclization.

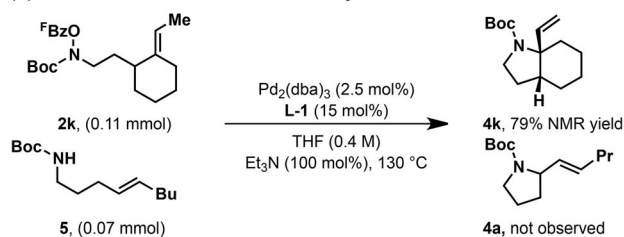


[a] Et₃N (300 mol%) was used. Alkene geometry of substrates: **2o**, Z; **2p**, Z; **2q**, Z; **2r**, 3:1 Z:E; **2s**, E; **2t**, E; **2u**, E; **2v**, E; **2w**, E; **2x**, E.

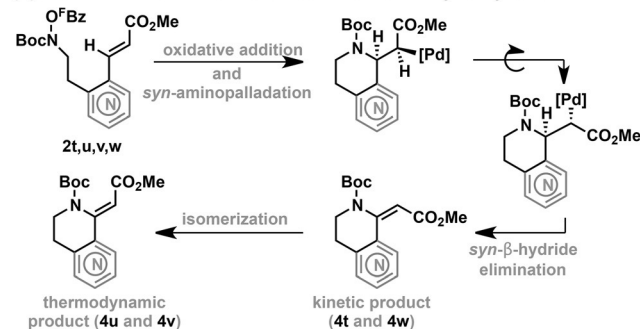
2u was run to partial conversion (3 h), **4u** was generated in a 14:1 *E*:*Z* ratio, such that isomerization of the initially formed product likely accounts for the geometry of isolated material (see the SI for details).^[16] As with Class 1 and 2 aza-Heck processes, protodecarboxylation of the pentafluorobenzoate leaving group likely plays a key role in the processes described here. ¹⁹F and ¹H NMR studies revealed that this process is intimately linked to turnover; in the cyclization of **CF₃-2i**, C₆F₅H was formed at the same rate as cyclization product **CF₃-4i** (Scheme 2C). Accordingly, we suggest that a cationic aza-Pd^{II} intermediate is required for cyclization and access to this is driven by triethylammonium mediated protodecarboxylation of pentafluorobenzoate, a process that we have shown to be facile.^[10f] The efficiency of the PA-Ar ligand system is consistent with studies by Hanley and Hartwig where electron poor and bulky P-based ligands were found to accelerate alkene aza-palladation in other contexts.^[17] For the current processes, the synergy of a bulky ligand system and a bulky N-protecting group may be especially beneficial, and this might account for the higher efficiencies observed for *N*-Boc protected systems. The conformational control that this unit provides is also likely a key factor.

The aza-Heck process can also be adapted to cascade sequences where the alkyl-Pd^{II} intermediate formed upon alkene amino-palladation is diverted to a subsequent C–C bond forming event. For example, aza-Heck–Heck cyclization of bis-alkenyl system **2y** delivered spirocycle **4y** in 68 % yield (Scheme 3A). We have also assessed the feasibility of partially intermolecular cascade processes as a means of providing a modular and flexible approach to alkene 1,2-carboamination (Scheme 3B).^[10f,18,19] Cyclization of **6a** in the

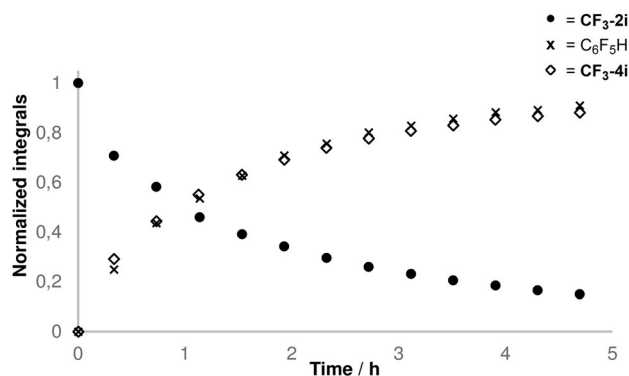
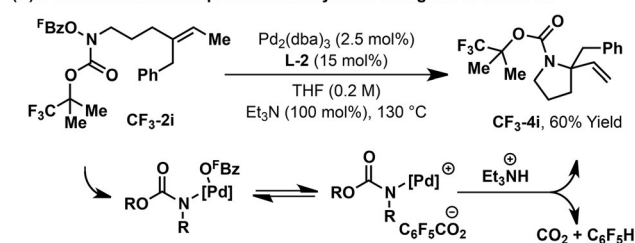
(A) The N-O bond is an internal oxidant only:



(B) Rationale for stereochemical outcomes of *trans*-acrylate systems:



(C) Pentafluorobenzoate protodecarboxylation is aligned to turnover:

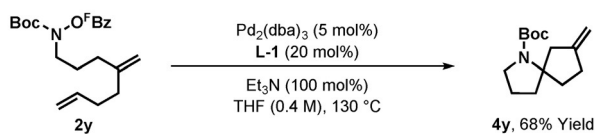


Scheme 2. Key mechanistic observations.

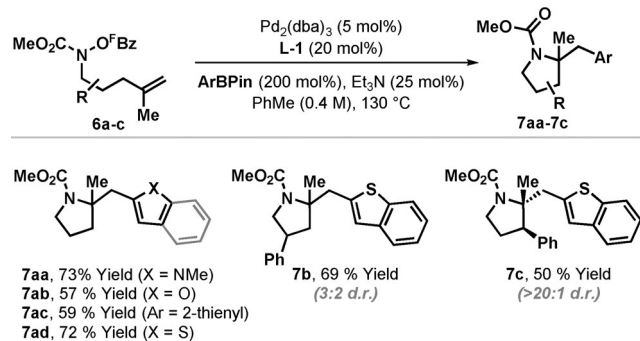
presence of *N*-methylindole-2-boronic acid pinacol ester (200 mol %) provided 1,2-amino-arylation product **7aa** in 73 % yield. Other electron rich heteroaryl boronic esters were also able to trap the alkyl-Pd^{II} intermediate efficiently to give 1,2-amino-arylation products **7ab–7ad**.

In summary, we outline highly efficient aza-Heck cyclizations of activated *N*-hydroxycarbamates. The chemistry is reliant on PA-Ar ligand systems, and, importantly, these allow, for the first time, efficient non-biased 6-*exo* cyclizations. Further generalization of the approach, including the development of asymmetric variants^[20] and other classes of cascade reaction, will be reported in due course. In broader terms, the studies described here have uncovered a new entry to aza-Pd^{II} intermediates via N–O oxidative addition. Given

(A) An intramolecular alkene 1,2-carboamination reaction:



(B) Two component alkene 1,2-aminoarylation reactions:



Scheme 3. Cascade processes.

the now broad utility of oxime ester derived imino-Pd^{II} intermediates,^[10,21] application of this unusual initiation mode^[9] in the design of other redox neutral C–N bond formations can be anticipated.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aza-Heck reaction · cascade reactions · N-heterocycles · palladium

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